

METHOD AND APPARATUS FOR AUTOMATING AN ATMOSPHERIC  
PRESSURE IONIZATION (API) SOURCE FOR MASS SPECTROMETRY

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of application Ser.  
No. 09/507,423, filed February 18, 2000.

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to mass spectrometry and the analysis of chemical samples, and more particularly to the apparatuses and methods for the automated preparation and introduction of samples into an atmospheric pressure ionization (API) mass spectrometer. Described herein is a system utilizing a multiple part capillary device with a robot for use in mass spectrometry (particularly with ionization sources) to transport ions to the mass spectrometer for analysis therein.

BACKGROUND OF THE PRESENT INVENTION

The present invention relates to a means of delivering ions to a mass spectrometer. Mass spectrometry is an important tool in the analysis of a wide range of chemical compounds. Specifically, mass spectrometers can be used to determine the molecular weight of sample compounds. The analysis of samples by mass spectrometry

1 consists of three main steps -- formation of ions from sample  
2 material, mass analysis of the ions to separate the ions from one  
3 another according to ion mass, and detection of the ions. A  
4 variety of means exist in the field of mass spectrometry to perform  
5 each of these three functions. The particular combination of means  
6 used in a given spectrometer determine the characteristics of that  
7 spectrometer.

8 To mass analyze ions, for example, one might use a magnetic  
9 (B) or electrostatic (E) analyzer. Ions passing through a magnetic  
10 or electrostatic field will follow a curved path. In a magnetic  
11 field the curvature of the path will be indicative of the momentum-  
12 to-charge ratio of the ion. In an electrostatic field, the  
13 curvature of the path will be indicative of the energy-to-charge  
14 ratio of the ion. If magnetic and electrostatic analyzers are used  
15 consecutively, then both the momentum-to-charge and energy-to-  
16 charge ratios of the ions will be known and the mass of the ion  
17 will thereby be determined. Other mass analyzers are the  
18 quadrupole (Q), the ion cyclotron resonance (ICR), the time-of-  
19 flight (TOF), and the quadrupole ion trap analyzers.

20 Before mass analysis can begin, however, gas phase ions must  
21 be formed from sample material. If the sample material is  
22 sufficiently volatile, ions may be formed by electron ionization

(EI) or chemical ionization (CI) of the gas phase sample molecules. For solid samples (e.g. semiconductors, or crystallized materials), ions can be formed by desorption and ionization of sample molecules by bombardment with high energy particles. Secondary ion mass spectrometry (SIMS), for example, uses keV ions to desorb and ionize sample material. In the SIMS process a large amount of energy is deposited in the analyte molecules. As a result, fragile molecules will be fragmented. This fragmentation is undesirable in that information regarding the original composition of the sample -- e.g., the molecular weight of sample molecules -- will be impossible to determine.

For more labile, fragile molecules, other ionization methods now exist. The plasma desorption (PD) technique was introduced by Macfarlane et al. in 1974 (Macfarlane, R. D.; Skowronski, R. P.; Torgerson, D. F., *Biochem. Biophys. Res Commun.* 60 (1974) 616). Macfarlane et al. discovered that the impact of high energy (MeV) ions on a surface, like SIMS would cause desorption and ionization of small analyte molecules, however, unlike SIMS, the PD process also results in the desorption of larger, more labile species -- e.g., insulin and other protein molecules.

Lasers have been used in a similar manner to induce desorption of biological or other labile molecules. See, for example,

1 VanBreeman, R.B.: Snow, M.: Cotter, R.J., *Int. J. Mass Spectrom.*  
2 *Ion Phys.* 49 (1983) 35; Tabet, J.C.; Cotter, R.J., *Anal. Chem.* 56  
3 (1984) 1662; or Olthoff, J.K.; Lys, I.: Demirev, P.: Cotter, R.  
4 J., *Anal. Instrument.* 16 (1987) 93. Cotter et al. modified a CVC  
5 2000 TOF mass spectrometer for infrared laser desorption of  
6 involatile biomolecules, using a Tachisto (Needham, Mass.) model  
7 215G pulsed carbon dioxide laser. The plasma or laser desorption  
8 and ionization of labile molecules relies on the deposition of  
9 little or no energy in the analyte molecules of interest. The use  
10 of lasers to desorb and ionize labile molecules intact was enhanced  
11 by the introduction of matrix assisted laser desorption ionization  
12 (MALDI) (Tanaka, K.; Waki, H.; Ido, Y.; Akita, S.; Yoshida, Y.;  
13 Yoshica, T., *Rapid Commun. Mass Spectrom.* 2 (1988) 151 and Karas,  
14 M.; Hillenkamp, F., *Anal. Chem.* 60 (1988) 2299). In the MALDI  
15 process, an analyte is dissolved in a solid, organic matrix. Laser  
16 light having a wavelength that is absorbed by the solid matrix but  
17 not by the analyte is used to excite the sample. Thus, the matrix  
18 is excited directly by the laser, and the excited matrix sublimates  
19 into the gas phase carrying with it the analyte molecules. The  
20 analyte molecules are then ionized by proton, electron, or cation  
21 transfer from the matrix molecules to the analyte molecules. This  
22 process, MALDI, is typically used in conjunction with time-of-

1 flight mass spectrometry (TOFMS) and can be used to measure the  
2 molecular weights of proteins in excess of 100,000 daltons.

3 Recently, MALDI has been especially gaining acceptance as a  
4 way to ionize large molecules such as proteins. MALDI requires  
5 that samples applied to the surface of a sample support must be  
6 introduced into the vacuum system of the mass spectrometer.  
7 According to the prior art, a relatively large number of sample are  
8 introduced together on a support, and the sample support is moved  
9 within the vacuum system in such a way that the required sample is  
10 situated specifically in the focus of the laser's lens system. The  
11 analyte samples are placed on a sample support in the form of small  
12 drops of a solution, which dry very quickly and leave a sample spot  
13 suitable for MALDI. Normally a matrix substance is added to the  
14 solution for the MALDI process and the sample substances are  
15 encased in the crystals when the matrix substance crystallizes  
16 while drying. There are other methods known in the prior art, such  
17 as the application of sample substances to an already applied and  
18 dried matrix layer.

19 Current methods use visual control of the sample spots via  
20 microscopic observation. Thus, these are not truly automated.  
21 True automation opens up the possibility of processing large  
22 numbers of samples. It is well established within the art that

1 microtiter plates are used for parallel processing of many samples.  
2 The body size of these plates is 80 by 125 millimeters, with a  
3 usable surface of 72 by 108 millimeters. There are commercially  
4 available sample processing systems which work with microtiter  
5 plates of this size. These originally contained 96 small  
6 exchangeable reaction vials in a 9mm grid on a usable surface of 72  
7 by 108 millimeters. Today, plates of the same size with 384  
8 reaction wells imbedded solidly in plastic in a 4.5 mm grid have  
9 become standard.

10 The use of Atmospheric pressure ionization (API) is also well  
11 known in the prior art. Typically, analyte ions are produced from  
12 liquid solution at atmospheric pressure. One of the more widely  
13 used methods, known as electrospray ionization (ESI), was first  
14 suggested by Dole et al. (M. Dole, L.L. Mack, R.L. Hines, R.C.  
15 Mobley, L.D. Ferguson, M.B. Alice, *J. Chem. Phys.* 49, 2240, 1968).  
16 In the electrospray technique, analyte is dissolved in a liquid  
17 solution and sprayed from a needle. The spray is induced by the  
18 application of a potential difference between the needle (where the  
19 liquid emerges) and a counter electrode. By subjecting the sample  
20 liquid to a strong electric field, it becomes charged, and as a  
21 result, it "breaks up" into smaller particles if the charge imposed  
22 on the liquid's surface is strong enough to overcome the surface

1 tension of the liquid (i.e., as the particles attempt to disperse  
2 the charge and return to a lower energy state). This results in  
3 the formation of finely charged droplets of solution containing  
4 analyte molecules. These droplets further evaporate leaving behind  
5 bare charged analyte ions.

6 Electrospray mass spectrometry (ESMS) was introduced by  
7 Yamashita and Fein (M. Yamashita and M.B. Fein, *J. Phys. Chem.* 88,  
8 4671, 1984). To establish this combination of ESI and MS, ions had  
9 to be formed at atmospheric pressure, then introduced into the  
10 vacuum system of a mass analyzer via a differentially pumped  
11 interface. The combination of ESI and MS affords scientists the  
12 opportunity to mass analyze a wide range of samples, and ESMS is  
13 now widely used primarily in the analysis of biomolecules (e.g.  
14 proteins) and complex organic molecules.

15 In the intervening years a number of means and methods useful  
16 to ESMS and API-MS have been developed. Specifically, a great deal  
17 of work has focused on sprayers and ionization chambers. In  
18 addition to the original electrospray technique, pneumatic assisted  
19 electrospray, dual electrospray, and nano electrospray are now also  
20 widely available. Pneumatic assisted electrospray (A.P. Bruins,  
21 T.R. Covey, and J.D. Henion, *Anal. Chem.* 59, 2642, 1987) uses  
22 nebulizing gas flowing past the tip of the spray needle to assist

1 in the formation of droplets. The nebulization gas assists in the  
2 formation of the spray and thereby makes the operation of ESI  
3 easier. Nano electrospray (M.S. Wilm, M. Mann, *Int. J. Mass*  
4 *Spectrom. Ion Processes* 136, 167, 1994) employs a much smaller  
5 diameter needle than the original electrospray. As a result the  
6 flow rate of sample to the tip is lower and the droplets in the  
7 spray are finer. However, the ion signal provided by nano  
8 electrospray in conjunction with MS is essentially the same as with  
9 the original electrospray. Nano electrospray is therefore much  
10 more sensitive with respect to the amount of material necessary to  
11 perform a given analysis.

12 Sample preparation robots (e.g. Gilson) have been used in the  
13 prior art for the automated injection of sample aliquots into an  
14 ESI source. In such a case, solution is pumped continuously from  
15 a reservoir to the sprayer of an ESI source. Sample aliquots are  
16 injected into this solution stream and are thereby carried through  
17 a transfer line to the sprayer.

18 Many other ion production methods might be used at atmospheric  
19 or elevated pressure. For example, MALDI has recently been adapted  
20 by Victor Laiko and Alma Burlingame to work at atmospheric pressure  
21 (Atmospheric Pressure Matrix Assisted Laser Desorption Ionization,  
22 poster #1121, 4<sup>th</sup> International Symposium on Mass Spectrometry in



1 the Health and Life Sciences, San Francisco, Aug. 25 - 29, 1998)  
2 and by Standing et al. at elevated pressures (Time of Flight Mass  
3 Spectrometry of Biomolecules with Orthogonal Injection +  
4 Collisional Cooling, poster #1272, 4<sup>th</sup> International Symposium on  
5 Mass Spectrometry in the Health and Life Sciences, San Francisco,  
6 Aug. 25 - 29, 1998; and Orthogonal Injection TOFMS *Anal. Chem.*  
7 71(13), 452A (1999)). The benefit of adapting ion sources in this  
8 manner is that the ion optics and mass spectral results are largely  
9 independent of the ion production method used.

10 An elevated pressure ion source always has an ion production  
11 region (where ions are produced) and an ion transfer region (where  
12 ions are transferred through differential pumping stages and into  
13 the mass analyzer). The ion production region is at an elevated  
14 pressure -- most often atmospheric pressure -- with respect to the  
15 analyzer.

16 In much of the prior art the ion production region will often  
17 include an ionization "chamber". In an ESI source, for example,  
18 liquid samples are "sprayed" into the "chamber" to form ions. The  
19 design of the ionization chamber used in conjunction with API-MS  
20 has had a significant impact on the availability and use of these  
21 ionization methods with MS. Prior art ionization chambers are  
22 inflexible in that a given ionization chamber can be used readily

1 with only a single ionization method and a fixed configuration of  
2 sprayers. For example, in order to change from a simple  
3 electrospray method to a nano electrospray method of ionization,  
4 one had to remove the electrospray ionization chamber from the  
5 source and replace it with a nano electrospray chamber (see also,  
6 Gourley et al. United States Pat. No. 5,753,910, entitled Angled  
7 Chamber Seal for Atmospheric Pressure Ionization Mass  
8 Spectrometry). In a co-pending application entitled Ionization  
9 Chamber For Atmospheric Pressure Ionization, this problem is  
10 addressed by disclosing an API ionization chamber providing  
11 multiple ports for employing multiple devices in a variety of  
12 combinations (e.g., any type of sprayer, lamp, microscope, camera  
13 or other such device in various combinations). Further, any given  
14 sprayer may produce ions in a manner that is synchronous or  
15 asynchronous with the spray from any or all of the other sprayers.  
16 By spraying in an asynchronous manner, analyte from a multitude of  
17 inlets may be sampled in a multiplexed manner.

18 Analyte ions produced via an API method need to be transported  
19 from the ionization region through regions of differing pressures  
20 and ultimately to a mass analyzer for subsequent analysis (e.g.,  
21 via TOFMS, Fourier transform mass spectrometry (FTMS), etc.). In  
22 prior art sources, this was accomplished through use of a small

1 orifice or capillary tube between the ionization region and the  
2 vacuum region. An example of such a prior art capillary tube is  
3 shown in FIG. 1. As depicted, capillary 7 comprises a generally  
4 cylindrical glass tube 2 having an internal bore 4. The ends of  
5 capillary 7 include a metal coating (e.g., platinum, copper, etc.)  
6 to form conductors 5 which encompass the outer surface of capillary  
7 7 at its ends, leaving a central aperture 6 such that the entrance  
8 and exit to internal bore 3 are left uncovered. Conductors 5 may  
9 be connected to electrical contacts (not shown) in order to  
10 maintain a desired space potential at each end of capillary 7. In  
11 operation, a first electrode (one of conductors 5) of capillary 7  
12 may be maintained at an extreme negative potential (e.g., -4,500V),  
13 while the other electrode (the other of conductors 5), which may  
14 form the first stage of a multi-stage lensing system for the final  
15 direction of the ions to the spectrometer, may be maintained at a  
16 positive potential (e.g., 160 volts).

17 It is often observed that the capillaries used in MS analysis  
18 acquire deposits over time. Therefore, through normal operation  
19 the capillaries need to be regularly cleaned or even replaced. To  
20 do so, the MS system must be turned off before the capillary can be  
21 removed -- requiring the pumps to be shut down and the vacuum  
22 system to be broken -- thereby rendering the system unavailable for

1 hours and even days at a time.

2 More recently, Lee et al. U.S. Pat. No. 5,965,883 attempted to  
3 solve this problem in the manner shown by FIG. 2. Shown in FIG. 2  
4 is capillary 8 which comprises an outer capillary sleeve 9  
5 surrounding an inner capillary tube 10. Sleeve 9 has substantially  
6 cylindrical inner surface 11 and outer surface 14. Similarly, tube  
7 10 has substantially cylindrical inner surface 12 and outer surface  
8 13. The innermost channel, or bore, of capillary 8 is  
9 substantially formed by inner surface 12 of tube 10. Capillary 8  
10 is substantially radially symmetrical about its central  
11 longitudinal axis 15 extending from an upstream end 16 to a  
12 downstream end 17. At each end, capillary 8 has conductive end  
13 caps 18 comprising the unitary combination of a tubular body having  
14 cylindrical inner surface 20 and outer surface 21 and an end plate  
15 22 having inner surface 23 and outer surface 24 with a central  
16 aperture. The tubular body of end cap 18 encompasses and is in  
17 circumferential engagement with a reduced diameter portion 25 of  
18 sleeve 9 adjacent to the respective ends of capillary 8, such that  
19 the external diameter of end cap 18 is substantially the same as  
20 the external diameter of sleeve outer surface 14.

21 In order to remove tube 10, end cap 18 at the upstream end of  
22 capillary 8 is first removed. A removal tool (not shown) is

1 inserted into the tube as to engage the tube's inner surface 12.  
2 It is further suggested by the prior art that in order to remove  
3 tube 10 it may be necessary to apply a slight torque orthogonal to  
4 axis 15, or other appropriate means such as bonding a removal tool  
5 to the tube using an adhesive. Once the tube is withdrawn, a  
6 replacement tube may be inserted into sleeve 9. However, this too  
7 is difficult and cumbersome, requiring tools to remove and replace  
8 the inner capillary tube.

9 Such prior art designs for the transfer capillary have  
10 inherent limitations relating to geometry, orientation, and ease of  
11 use. The capillary according to these prior art designs is  
12 substantially fixed in the source. Only if the instrument -- or at  
13 least the source -- is vented to atmospheric pressure can the  
14 capillary be removed. The geometric relation of the capillary is  
15 therefore fixed with respect to the source and all its components.  
16 This implies that the ion production means - e.g. an electrospray  
17 needle, atmospheric pressure chemical ionization sprayer, or MALDI  
18 probe - must be positioned with respect to the capillary entrance.  
19 In order to change from one ion production means to another - e.g.  
20 from an electrospray needle to a nano electrospray needle - the  
21 first means must be removed from the vicinity of the capillary  
22 entrance and the second must then be properly positioned with

1 respect to the capillary entrance. For any production means, there  
2 will be an optimum geometry between the means and the capillary  
3 entrance at which the ion current passing into the analyzer is  
4 maximized. To achieve this optimum, a positioning means must be  
5 provided for positioning the ion production means with respect to  
6 the capillary entrance. This might take the form of precision  
7 machined components, a translation stage on which the ion  
8 production means is mounted, or some other device. If the ion  
9 production means is required or desired to be remote from the  
10 source, a long, fixed length capillary would have to be produced  
11 and installed (in a fixed position) in the source.

12 Another limitation of prior art capillaries relates to the  
13 orientation of the capillary bore with respect to the ion  
14 production means. Such orientation can be important for the  
15 operation of the source. One major consideration in the operation  
16 of an electrospray source is the formation of large droplets from  
17 the analyte solution at the spray needle. Such droplets do not  
18 readily evaporate. If these droplets enter the capillary, they may  
19 cause the capillary to become contaminated with a residue of  
20 analyte molecules and salts. In view of this, Apfel et al. in US  
21 patents 5,495,108 and 5,750,988 describe apparatuses for API  
22 sources wherein the axis of the bore of the capillary 110 is at an

1 angle of  $90^\circ$  with respect the axis of the bore of the spray needle  
2 111, as depicted in FIG. 3. According to Apfel et al., certain  
3 experimental conditions lead to the production of large droplets by  
4 the spray needle. These large droplets will move away from the  
5 spray needle along the axis of the sprayer. However, an electric  
6 field between the spray needle and the capillary will cause ions  
7 formed from the spray to move towards the capillary. In this way,  
8 the ions are separated from the spray droplets and the droplets do  
9 not enter the capillary. However, this orientation is fixed in the  
10 prior art source of Apfel. To change this orientation, one would  
11 have to move the spray needle.

12 Prior art capillaries are further limited in the geometry of  
13 the capillary bore. That is, prior art capillaries, as depicted in  
14 FIGs. 1-3, are substantially straight (i.e., cylindrically  
15 symmetric) and fixed (i.e., the geometry of the capillary and its  
16 bore is fixed at the time of manufacture). However, as described  
17 in the co-pending application METHOD AND APPARATUS FOR A MULTIPLE  
18 PART CAPILLARY DEVICE FOR USE IN MASS SPECTROMETRY Serial No.  
19 09/507,423 a capillary which can be cleaned or replaced without  
20 the need to shut down the entire mass spectrometer in which it  
21 resides now exists. The use of this capillary within the system  
22 described herein allows ionization to occur within the MALDI tray

1 as opposed to occurring within the vacuum.

2 Others have disclosed atmospheric pressure matrix-assisted  
3 laser desorption/ionization (AP-MALDI). Laiko et al. disclose an  
4 AP-MALDI apparatus for the transfer of ions from an atmospheric  
5 pressure ionization region to a high vacuum region, which is  
6 pneumatically assisted (PA) by a stream of nitrogen gas. (Victor V.  
7 Laiko, Michael A. Baldwin and Alma L. Burlingame, "Atmospheric  
8 Pressure Matrix-Assisted Laser Desorption/Ionization Mass  
9 Spectrometry", Analytical Chemistry, Vol. 72, No. 4, February 4,  
10 2000). The invention of matrix-assisted laser  
11 desorption/ionization (MALDI) and electrospray ionization (ESI) are  
12 considered the most powerful tools for detection, identification,  
13 and characterization of biopolymers such as peptides, proteins, and  
14 DNA. MALDI and ESI enable the production of intact heavy molecular  
15 ions from a condensed phase, where MALDI is for solids and ESI is  
16 for liquids. Although, MALDI's target material density drops  
17 rapidly after laser desorption, from a high value characteristic of  
18 the initial solid phase to a very low value. Hence, a new  
19 ionization source combines atmospheric pressure and MALDI, which  
20 was called atmospheric pressure (AP) MALDI. AP-MALDI produces a  
21 uniform ion cloud under atmospheric pressure conditions. The  
22 apparatus disclosed in Laiko, i.e., for PA-AP-MALDI, is readily



1 interchangeably with electrospray ionization on an orthogonal  
2 acceleration TOF mass spectrometer. According to Laiko, PA-AP-  
3 MALDI can detect low femtomole amounts of peptides in mixtures with  
4 good signal-to-noise ratio and with less discrimination for the  
5 detection of individual peptides in a protein digest. Thus, total  
6 sample consumption is higher for PA-AP-MALDI than vacuum MALDI, as  
7 the transfer of ions into the vacuum system is relatively  
8 inefficient.

9 Yet another high throughput MALDI elevated pressure mass  
10 spectrometry technique and apparatus is disclosed by Shevchenko et  
11 al. ("MALDI Quadrupole Time-of-Flight Mass Spectrometry: A Powerful  
12 Tool for Proteomic Research", Analytical Chemistry, Vol. 72, No. 9,  
13 May 1, 2000). More particularly, Shevchenko et al. disclose use of  
14 a MALDI QqTOF mass spectrometer to achieve high mass resolution and  
15 accuracy in the identification of proteins. The apparatus  
16 disclosed by Shevchenko includes interfacing an orthogonal  
17 injection TOF MS to a hybrid quadrupole TOF MS (QqTOF) to form a  
18 MALDI QqTOF instrument, whereby a collisional damping interface  
19 cools the ions before they enter the analytical quadrupole Q.  
20 According to Shevchenko, once the ions are cooled, they can be  
21 transported through the quadrupoles more efficiently for  
22 measurement of the whole mass spectrum. A precursor ion can be

1 selected in the quadrupole Q and fragmented in the collision cell  
2 q. Measurement of the product ions in the TOF section then  
3 provides a MS/MS spectrum of the selected precursor, thus carrying  
4 out both peptide mass mapping and MS/MS measurement on the same  
5 target in the same experiment. This process provides a high mass  
6 selection of precursor ions, precise tuning of the collision  
7 energy, and a much simplified calibration procedure. Also,  
8 Schevchenko et al. suggest that such an analytical approach lends  
9 itself to automation in obtaining MALDI spectra. However,  
10 Schevchenko et al. are silent as to how this might be achieved.

11 Also, Franzen et al. U.S. Patent No. 5,663,561 (Franzen)  
12 teaches a device and method for the desorption and ionization of  
13 labile substance molecules at atmospheric pressure by MALD followed  
14 by chemical ionization (APCI). The method of Franzen consists of  
15 desorbing the analyte substances, which are mixed with decomposable  
16 substances (matrix substances) in solid form on a solid support, by  
17 laser irradiation at atmospheric pressure into a gas stream, and to  
18 add sufficient ions for proton transfer reactions to the gas  
19 stream. The objective of the method and apparatus of Franzen et  
20 al. is to transfer large molecules on solid sample support from  
21 solid state to a state of ionized gas phase molecules to be  
22 subjected to mass spectrometric analysis in an efficient manner.

1       The system disclosed in Franzen et al. generates ions from  
2       macromolecular substances in an area outside the vacuum, instead of  
3       within the vacuum, and separates the ionization process from the  
4       desorption process. Since new development of ion transfer from  
5       atmospheric pressure have become possible, external ionization has  
6       become effective and relatively economical. Thus, Franzen et al.  
7       recognized the problem of evaporating the non-volatile analyte  
8       substances into the surrounding gas. Therefore, the method and  
9       apparatus of Franzen et al. support the desorption process by  
10      photolytic and thermolytic processes triggered by laser photons.  
11      Consequently, the matrix material would decompose explosion-like  
12      into small gas molecules which can blast the analyte molecules into  
13      the surrounding gas. Then, the matrix molecules in the photolytic  
14      and thermolytic processes are broken down into smaller molecules.  
15      According to Franzen et al., if a matrix substance is selected in  
16      such a way that the product of its decomposition is gaseous in its  
17      normal state, the large, embedded analyte molecules would be  
18      catapulted into the gas phase. Of course, the matrix material then  
19      has to be selected such that the transfer of heat to the analyte  
20      molecules is minimal.

21       Moreover, in each of these systems, the samples are positioned  
22       outside of the vacuum system of the mass spectrometer for  
23       ionization (e.g., a MALDI target, sample plate, etc.). The present  
24       invention recognizes this and provides a simple and efficient  
25       method and apparatus for ionizing samples and introducing the

1 sample ions into a mass spectrometer with the sample positioned  
2 outside of the vacuum system of the mass spectrometer.

3 Also, it has been recognized that a need exists for a simple,  
4 fast, efficient and reliable means of integrating a robot with  
5 various ionization sources for automating the preparation and  
6 introduction of samples into a mass spectrometer, and more  
7 particularly into an atmospheric pressure MALDI mass spectrometer.  
8 The present invention provides a novel solution to this problem.

9  
10 SUMMARY OF THE INVENTION

11 The present invention relates generally to mass spectrometry  
12 and the analysis of chemical samples, and more particularly to the  
13 robotic interface of sample introduction into a source region of a  
14 mass spectrometer using specially designed multiple part capillary  
15 tubes.

16 It is a first object of the invention to provide an improved  
17 method and apparatus for the automatic preparation and introduction  
18 of samples into a mass spectrometer for subsequent mass analysis.

19 It is another object of the invention to provide a method and  
20 apparatus for the automatic preparation and introduction of samples  
21 maintained at atmospheric pressure (i.e., outside the vacuum  
22 system) into a mass spectrometer for subsequent mass analysis.

23 It is yet another object of the invention to provide a method  
24 and apparatus whereby a single robot is used for the automatic  
25 preparation and introduction of samples into a mass spectrometer

1 for subsequent mass analysis.

2 It is still a further object of the invention to provide a  
3 method and apparatus for the automatic preparation and introduction  
4 of samples into a mass spectrometer from a plurality of  
5 electrospray ionization (ESI) sprayers for subsequent mass  
6 analysis.

7 Yet another aspect of the present invention is to provide a  
8 capillary for use in an ion source having improved flexibility and  
9 accessibility over prior art designs. A capillary according to the  
10 invention consists of at least two sections joined together end to  
11 end such that gas and sample material in the gas can be transmitted  
12 through the capillary across a pressure differential. The  
13 capillary is intended for use in an ion source wherein ions are  
14 produced at an elevated pressure and transported by the capillary  
15 into a vacuum region of the source.

16 Still another object of the invention is to allow for the  
17 removal of one or more sections of the capillary (for cleaning or  
18 replacement) without having to shut down the pumping system of the  
19 instrument to which it is attached. These sections may be made of  
20 different materials -- e.g., glass, metal, composite, etc. -- which  
21 may be either electrically conducting or non-conducting. Also,  
22 each section of the capillary according to the invention does not  
23 have to be straight or rigid, rather, one or more of the sections  
24 may be flexible such that it (or they) can bend in any direction.

25 Another object of the invention is to utilize a multiple part

1 capillary which offers improved flexibility in its geometric  
2 orientation with respect to other devices in the ionization source  
3 -- especially the ion production means. For example, the axis of  
4 the bore or "channel" of the capillary at the capillary entrance  
5 might be positioned at any angle with respect to the ion production  
6 means. This angle, as discussed in Apfel U.S. Patent Nos.  
7 5,495,108 and 5,750,988 can be important, for example, in the  
8 separation of spray droplets from desolvated analyte ions. Also  
9 according to the present invention, the entrance section of the  
10 capillary might be modified or exchanged before or during  
11 instrument operation to effect a change in the orientation of the  
12 entrance with respect to the ion production means or other device.

13 This flexibility applies to the translational position of the  
14 entrance of the capillary as well as its angular orientation. That  
15 is, the position of the entrance of the capillary might be changed  
16 before or during instrument operation by either modification or  
17 exchange of the first section of the capillary. This allows for  
18 the transmission of ions from a variety of locations either near or  
19 removed from the immediate location of the source.

20 Still another object of the present invention is to utilize a  
21 multipurpose multiple part capillary wherein the bore or "channel"  
22 of one or more of the sections of the multiple part capillary may  
23 comprise any useful geometry (i.e., straight, helical, wave-like,  
24 etc.). For instance, it may be particularly useful to have an  
25 inner channel of helical geometry. This will cause larger

1 particles (e.g., droplets from electrospray) to collide with the  
2 walls of the capillary, while allowing smaller particles (e.g.,  
3 fully desolvated electrosprayed ions) to pass through the  
4 capillary. Note that the geometry of the bore may be, but is not  
5 necessarily, related to the outer surface of the capillary. That  
6 is, a capillary might have a cylindrically symmetric outer surface  
7 but have an inner bore which is helical.

8 Yet another purpose of the present invention is to provide a  
9 simple and efficient method and apparatus for integrating multiple  
10 source assemblies. A complete ion source may include a multitude  
11 of sub-assemblies. For example, an ion source might include an ion  
12 production means sub-assembly and vacuum sub-assembly. The ion  
13 production means sub-assembly might include a spray needle, its  
14 holder, a translation stage, etc. The vacuum sub-assembly might  
15 contain pumps, pumping restrictions, and ion optics for guiding  
16 ions into the mass analyzer. In prior art ion sources and MS  
17 instruments, the capillary would conventionally be integrated  
18 entirely in one sub-assembly -- the vacuum sub-assembly. As a  
19 result, significant effort is required in prior art systems to  
20 align the ion production means sub-assembly -- specifically the  
21 spray needle -- with the vacuum sub-assembly -- specifically the  
22 capillary entrance. The multiple part capillary according to the  
23 present invention eases the integration of such sub-assemblies by  
24 including capillary sections in each of the sub-assembly. The sub-  
25 assemblies are integrated by joining the capillary sections

1 together. Any necessary alignments are performed within a given  
2 sub-assembly -- e.g. alignment of the spray needle with the first  
3 section of capillary. This sub-assembly arrangement allows for the  
4 automation of a MALDI-TOF mass spectrometer.

5 It is a further purpose of the present invention to provide  
6 flexibility when using a particular mass spectrometer by providing  
7 efficient use of a plurality of ionization sources. For example,  
8 in combination with the ionization chamber described in co-pending  
9 application serial no. 09/263,659, entitled IONIZATION CHAMBER FOR  
10 ATMOSPHERIC PRESSURE IONIZATION MASS SPECTROMETRY, which is  
11 incorporated herein by reference, the present invention provides  
12 added flexibility for switching from one ionization source to  
13 another or from one sample to another. Specifically, the capillary  
14 according to the invention is capable of efficiently and accurately  
15 being used with multiple electrospray sources. In addition, the  
16 capillary according to the invention is useful in multiplexing.

17 Another purpose of the invention is to provide a multiple part  
18 capillary which can be used with chromatographic sample preparation  
19 (e.g., liquid chromatography, capillary electrophoresis, etc.).  
20 The effluent from such a chromatographic column may be injected  
21 directly or indirectly into one of the sprayers. A plurality of  
22 such chromatographic columns may be used in conjunction with a  
23 plurality of sprayers -- for example one sprayer per column. The  
24 presence of analyte in the effluent of any given column might be  
25 detected by any appropriate means, for example a UV detector. When



1 analyte is detected in this way, the sprayer associated with the  
2 column in question is "turned on" so that while analyte is present  
3 the sprayer is producing ions but otherwise the sprayer does not.  
4 If analyte is present simultaneously at more than one sprayer, the  
5 sprayers are multiplexed, as discussed above.

6 It is yet another purpose of the invention to allow a simple,  
7 fast, efficient and reliable means of integrating a robot with  
8 various ionization sources and techniques. The multiple part  
9 capillary disclosed herein allows such a means for integrating a  
10 robot with any of a variety of ionization sources, including  
11 elevated pressure and atmospheric pressure sources. The design of  
12 the multiple part capillary according to the present invention  
13 provides added versatility to the use of ionization chambers as  
14 well as to the use and performance of any new and existing  
15 ionization methods.

16 Further, the present system allows for the removal of one or  
17 more sections of the capillary (for cleaning or replacement)  
18 without having to shut down the pumping system or the instrument to  
19 which it is attached. The capillary according to the present  
20 invention can, among other things, be made from different  
21 materials, take on different sizes, shapes or forms, as well as  
22 perform different functions. Furthermore, to provide a fully  
23 automated system for the analysis of a variety of chemical species  
24 efficiently and cost effectively.

25 Other objects, features, and characteristics of the present

1 invention, as well as the methods of operation and functions of the  
2 related elements of the structure, and the combination of parts and  
3 economies of manufacture, will become more apparent upon  
4 consideration of the following detailed description with reference  
5 to the accompanying drawings, all of which form a part of this  
6 specification.

7  
8 BRIEF DESCRIPTION OF THE DRAWINGS

9 A further understanding of the present invention can be  
10 obtained by reference to a preferred embodiment set forth in the  
11 illustrations of the accompanying drawings. Although the  
12 illustrated embodiment is merely exemplary of systems for carrying  
13 out the present invention, both the organization and method of  
14 operation of the invention, in general, together with further  
15 objectives and advantages thereof, may be more easily understood by  
16 reference to the drawings and the following description. The  
17 drawings are not intended to limit the scope of this invention,  
18 which is set forth with particularity in the claims as appended or  
19 as subsequently amended, but merely to clarify and exemplify the  
20 invention.

21 For a more complete understanding of the present invention,  
22 reference is now made to the following drawings in which:

23 FIG. 1 shows a partial cut-away cross-sectional view of a  
24 prior art capillary comprising a unitary glass tube having a  
25 cylindrical outer surface and internal bore;

1 FIG. 2 shows a partial cut-away cross sectional view of  
2 another prior art capillary comprising a concentric outer capillary  
3 sleeve and inner capillary tube;

4 FIG. 3 shows a prior art spray chamber of a prior art  
5 electrospray ionization source wherein the channel of the spray  
6 needle is oriented orthogonal to the channel of the capillary;

7 FIG. 4 shows a preferred embodiment of a multiple part  
8 capillary according to the present invention;

9 FIG. 5 shows an alternate embodiment of the multiple part  
10 capillary, wherein the channel of the first section comprises a  
11 helical structure;

12 FIG. 6 shows an ESI sprayer needle oriented at an angle  $\theta$  with  
13 respect to the inlet to the channel and an angle  $\alpha$  with respect to  
14 the body of an embodiment of the multiple part capillary according  
15 to the present invention;

16 FIG. 7 shows an embodiment of the multiple part capillary  
17 according to the present invention as used with an ESI ionization  
18 source;

19 FIG. 8 shows a multiple part capillary according to the  
20 present invention as a means for integrating two source sub-  
21 assemblies;

22 FIG. 9 shows the multiple part capillary according to the  
23 present invention as a means for integrating a sample preparation  
24 robot with an API source for mass spectrometry;

25 FIG. 10 shows an embodiment of the multiple part capillary

1 according to the present invention as a means for integrating a  
2 sample preparation robot with an elevated pressure MALDI source for  
3 mass spectrometry; and

4 FIG. 11 shows a close-up view of the use of the multiple part  
5 capillary with a MALDI probe in accordance with the present  
6 invention.

7  
8 DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

9 As required, a detailed illustrative embodiment of the  
10 present invention is disclosed herein. However, techniques,  
11 systems and operating structures in accordance with the present  
12 invention may be embodied in a wide variety of sizes, shaped,  
13 forms and modes, some of which may be quite different from those  
14 in the disclosed embodiment. Consequently, the specific  
15 structural and functional details disclosed herein are merely  
16 representative, yet in that regard, they are deemed to afford the  
17 best embodiment for purposes of disclosure and to provide a basis  
18 for the claims herein which define the scope of the present  
19 invention.

20 The following presents a detailed description of a preferred  
21 embodiment of the present invention, as well as some alternate  
22 embodiments of the invention. As discussed above, the present  
23 invention relates generally to the mass spectroscopic analysis of  
24 chemical samples and more particularly to mass spectrometry.  
25 Specifically, an apparatus and method are described for transport

1 of ions to the mass spectrometer. Reference is herein made to  
2 the figures, wherein the numerals representing particular parts  
3 are consistently used throughout the figures and accompanying  
4 discussion.

5 With reference first to FIG. 4, shown is multiple part  
6 capillary 35 according to a preferred embodiment of the present  
7 invention. As depicted in FIG. 4, multiple part capillary 35  
8 comprises: first section 28 having capillary inlet end 26 and  
9 first channel 27; union 29 having o-ring 31; second section 33  
10 having second channel 32 and capillary outlet end 34; and metal  
11 coatings 30A and 30B. According to the preferred embodiment,  
12 first section 28 is connected to second section 33 by union 29.  
13 In the preferred embodiment, union 29 is substantially  
14 cylindrical having two coaxial bores, 60 and 61, and through hole  
15 62 of the same diameter as channels 26 and 32. In the preferred  
16 embodiment, section 28 and union 29 are composed of metal - e.g.  
17 stainless steel. The inner diameter of bore 60 and the outer  
18 diameter of section 28 are chosen to achieve a "press fit" when  
19 section 28 is inserted into bore 60. Because the press fit is  
20 designed to be tight, union 29 is thereby strongly affixed to  
21 section 28 and a gas seal is produced between union 29 and  
22 section 28 at the surface of the bore. The inner diameter of  
23 bore 61 is of slightly larger diameter than the outer diameter of  
24 section 33 (including metal coating 30A) so as to produce a "slip  
25 fit" between union 29 and section 33. A gas seal is established

1 between bore 61 and section 33 via o-ring 31. Electrical contact  
2 between metal coating 30A, union 29, and section 28 via direct  
3 physical contact between the three. Through hole 62 allows for  
4 the transmission of gas from entrance end 26 through to exit end  
5 34 of the capillary. Ideally, union 29 and sections 28 and 33  
6 are formed in such a way as to eliminate any "dead volume"  
7 between these components. To accomplish this, the ends of  
8 sections 28 and 33 are formed to be flush with the inner surface  
9 of union 29. Note that the body of section 33 - excluding metal  
10 coatings 30A and 30B - is composed of glass in the preferred  
11 embodiment. As a result, metal coating 30A - together with union  
12 29 and section 28 - can be maintained at a different electrical  
13 potential than metal coating 30B.

14 Alternatively, union 29, and sections 28 and 33 may be  
15 composed of a variety of materials conducting or non-conducting;  
16 the outer diameters of the sections may differ substantially from  
17 one another; the inner diameters of the sections may differ  
18 substantially from one another; either or both ends or any or all  
19 sections may be covered with a metal or other coating; rather  
20 than a coating, the ends or capillary sections may be covered  
21 with a cap composed of metal or other material; the capillary may  
22 be composed of more than two sections always with one fewer union  
23 than sections; and the union may be any means for removably  
24 securing the sections of capillary together and providing an  
25 airtight seal between these sections.

1 Each end of union 29 could comprise a generally cylindrical  
2 opening having an internal diameter slightly larger than the  
3 external diameter of the end of the capillary section which is to  
4 be inserted therein. In such an embodiment, a gas seal is made  
5 with each capillary section via an o-ring similar to o-ring 31.  
6 As a further alternative, one might use springs to accomplish  
7 electrical contact between union 29 and sections 28 and 33. In  
8 this case a conducting spring would be positioned in union 29  
9 adjacent to o-ring 31.

10 Moreover, in a preferred embodiment of the capillary  
11 according to the invention, the length of first section 28 is  
12 less than (even substantially less than) the length of second  
13 section 33. More specifically, the dimensions of first section  
14 28 and second section 33 are such that within a range of desired  
15 pressure differentials across capillary 35, a gas flow rate  
16 within a desired range will be achieved. For example, the length  
17 of second section 33 and the internal diameter of second channel  
18 32 are such that the gas transport across second section 33 alone  
19 (i.e., with first section 28 removed) at the desired pressure  
20 differential will not overload the pumps which generate the  
21 vacuum in the source chamber of the system. This allows the  
22 removal (e.g., for cleaning or replacement) of first section 28  
23 of capillary 35 without shutting down the pumping system of the  
24 mass spectrometer.

25 While the prior art, as depicted in FIG. 2, attempts to

1 accomplish removal, without shutting down the vacuum, it is  
2 difficult and cumbersome. As discussed previously, tools and  
3 adhesives may be required to remove and replace the capillary.  
4 The multiple part capillary according to the present invention  
5 provides a much simpler method and apparatus for accomplishing  
6 this result (i.e., without the use of adhesives, tools, etc.).

7 Turning next to FIG. 5, an alternate embodiment of capillary  
8 35 is shown wherein capillary section 28 has a serpentine  
9 internal channel 64. That is, the geometric structure of the  
10 internal channel of the capillary section is sinusoidal. Of  
11 course, other geometrical structures (i.e., helical, varying  
12 diameter, non-uniform, etc.) may be used in accordance with the  
13 invention. Having sinusoidal internal channel 64 causes larger  
14 particles -- such as droplets from an electrospray -- to collide  
15 with the walls of the channel and thereby not pass completely  
16 through the capillary. On the other hand, smaller particles --  
17 such as fully desolvated electrosprayed ions -- do not collide  
18 with the walls and pass completely through the capillary. The  
19 curved (or sinusoidal) geometry of channel 64 also increases the  
20 length of the channel, which provides the advantage of permitting  
21 a larger diameter channel. Such a larger diameter channel may be  
22 advantageous in that it may provide greater acceptance of sampled  
23 species (e.g., electrosprayed ions, etc.) at a given flow rate  
24 and pressure differential. Alternatively, a sinusoidal -- or any  
25 other geometry -- channel may be used in either first section 28



1 or second section 33, or both.

2 In accordance with the present invention, it is observed  
3 that the introduction of ions from an ionization means into the  
4 multiple part capillary of the invention may be accomplished at  
5 any angle of incidence between the ionization means and the inlet  
6 of the capillary. Referring now to FIG. 6, shown is an  
7 embodiment of the multiple part capillary according to the  
8 invention as used with an ESI sprayer 65 wherein axis 70 of  
9 sprayer 65 is oriented at angle  $\alpha$  66 with respect to axis 69 of  
10 the body of capillary 72. However, because channel 73 of  
11 capillary section 74 is curved, angle  $\theta$  67 between sprayer axis  
12 70 and axis 71 of channel entrance 68 can be substantially  
13 different than angle  $\alpha$  66. The embodiment shown in FIG. 6  
14 demonstrates that the capillary entrance angle  $\alpha$  66 may be any  
15 angle from  $0^\circ$  and  $180^\circ$ . The specific angle selected is dependent  
16 upon, among other things, the sample species being tested, the  
17 ionization source used, etc. As discussed above, the  
18 electrospray process results in the formation of charged droplets  
19 and molecular ions. The presence of large droplets in the spray  
20 can result in contamination of the capillary and generally poor  
21 instrument performance. One way of limiting the influence of  
22 large droplets on instrument performance is to spray away from  
23 the capillary entrance. That is, the spray needle is oriented so  
24 that it is not pointed directly at the capillary entrance. Large  
25 droplets formed in a source with such a geometry will tend to

1 move along the axis of the spray needle and not enter the  
2 capillary, whereas desolvated ions will be attracted to the  
3 capillary entrance by the electrostatic field between the spray  
4 needle and the capillary. Thus, in the embodiment of figure 6,  
5 smaller angles  $\alpha$  66 and  $\theta$  67 will tend to reduce the fraction of  
6 droplets that enter the capillary.

7 In any case, the sinusoidal geometry of channel 73 tends to  
8 limit the contamination of capillary 72 due to large droplets  
9 into section 74. Large droplets which enter the capillary will  
10 tend to strike the walls of channel 73 and not pass through to  
11 section 33. Section 74 can be removed from the system - by  
12 pulling it off along axis 69 - and cleaned without necessarily  
13 shutting the instrument or its vacuum system off.

14 Depicted in FIG. 7 is an ionization source which  
15 incorporates the multiple part capillary of the invention where  
16 the ion production means is an ESI sprayer device, shown as spray  
17 needle 36 in spray chamber 40. During normal operation of a  
18 preferred embodiment with an ESI source, sample solution is  
19 formed into droplets at atmospheric pressure by spraying the  
20 sample solution from spray needle 36 into spray chamber 40. The  
21 spray is induced by the application of a high potential between  
22 spray needle 36 and entrance 26 of first capillary section 28  
23 within spray chamber 40. Sample droplets from the spray  
24 evaporate while in spray chamber 40 thereby leaving behind an  
25 ionized sample material (i.e., sample ions). These sample ions

1 are accelerated toward capillary inlet 26 of channel 27 by an  
2 electric field generated between spray needle 36 and inlet 26 of  
3 first section 28 of capillary 35. These ions are transported  
4 through first channel 27 into and through second channel 32 to  
5 capillary outlet 34. As described above with regard to FIG. 4,  
6 first section 28 is joined to second section 33 in a sealed  
7 manner by union 29. The flow of gas created by the pressure  
8 differential between spray chamber 40 and first transfer region  
9 45 further causes the ions to flow through the capillary channels  
10 from the ionization source toward the mass analyzer.

11 Still referring to FIG. 7, first transfer region 45 is  
12 formed by mounting flange 48 on source block 54 where a vacuum  
13 tight seal is formed between flange 48 and source block 54 by o-  
14 ring 58. Capillary 35 penetrates through a hole in flange 48  
15 where another vacuum tight seal is maintained (i.e., between  
16 flange 48 and capillary 35) by o-ring 56. A vacuum is then  
17 generated and maintained in first transfer 45 by a pump (e.g., a  
18 roughing pump, etc., not shown). The inner diameter and length  
19 of capillary 35 and the pumping speed of the pump are selected to  
20 provide as high a rate of gas flow through capillary 35 as  
21 reasonably possible while maintaining a pressure of 1 mbar in the  
22 first transfer region 45. A higher gas flow rate through  
23 capillary 35 will result in more efficient transport of ions.

24 Next, as further shown in FIG. 7, first skimmer 51 is placed  
25 adjacent to capillary exit 34 within first transfer region 45.

1 An electric potential between capillary outlet end 34 and first  
2 skimmer 51 accelerates the sample ions toward first skimmer 51.  
3 A fraction of the sample ions then pass through an opening in  
4 first skimmer 51 and into second pumping region 43 where pre-  
5 hexapole 49 is positioned to guide the sample ions from the first  
6 skimmer 51 to second skimmer 52. Second pumping region 43 is  
7 pumped to a lower pressure than first transfer region 45 by pump  
8 53. Again, a fraction of the sample ions pass through an opening  
9 in second skimmer 52 and into third pumping region 44, which is  
10 pumped to a lower pressure than second pumping region 43 via pump  
11 53.

12 Once in third pumping region 44, the sample ions are guided  
13 from second skimmer 52 to exit electrodes 55 by hexapole 50.  
14 While in hexapole 50 ions undergo collisions with a gas (i.e., a  
15 collisional gas) and are thereby cooled to thermal velocities.  
16 The ions then reach exit electrodes and are accelerated from the  
17 ionization source into the mass analyzer for subsequent analysis.

18 Another application of the present invention is to provide a  
19 simple and efficient method and apparatus for integrating two  
20 source assemblies. As depicted in FIG. 8, a complete ion source  
21 may include a multitude of sub-assemblies. For example, ion source  
22 80 includes ion production means sub-assembly 81 and vacuum sub-  
23 assembly 82. The ion production means sub-assembly 81 includes,  
24 among other things, spray chamber 40 and spray needle 36. The  
25 vacuum sub-assembly 82 includes among other things, pump 53 and ion

1 optical elements 49-52 and 55 having pumping restrictions at  
2 elements 51 and 52 for guiding ions into the mass analyzer. In  
3 prior art sources and instruments, the capillary would be  
4 integrated entirely in one sub-assembly -- e.g., the vacuum sub-  
5 assembly 82. As a result, significant effort is required in prior  
6 art systems to align the ion production means sub-assembly 81  
7 (specifically the spray needle) with the vacuum sub-assembly 82  
8 (specifically the capillary entrance). The multiple part capillary  
9 according to the present invention can be used to ease the  
10 integration of such sub-assemblies by including capillary sections  
11 in each of the sub-assembly.

12 In the embodiment of FIG. 8, capillary section 28 is an  
13 integral component of ion production means sub-assembly 81 and  
14 capillary section 33 is an integral component of vacuum sub-  
15 assembly 82. Sub-assemblies 81 and 82 are integrated in part by  
16 joining capillary sections 28 and 33 together via union 29. Any  
17 necessary alignments are performed within a given sub-assembly  
18 (e.g., alignment of spray needle 36 with entrance 26 of channel  
19 27). In alternate embodiments, any variety of sub-assemblies might  
20 be integrated, in part or in whole, by including capillary sections  
21 in these sub-assemblies and subsequently joining these capillary  
22 sections together as discussed with respect to FIG. 8. Further,  
23 any number of sub-assemblies with any variety of functions might be  
24 used. Such functions might include ion production, desolvation of  
25 spray droplets via a heated capillary section, ion transfer to the

1 mass analyzer, etc. Clearly, any type of atmospheric pressure  
2 ionization means, including ESI, API MALDI, atmospheric pressure  
3 chemical ionization, nano electrospray, pneumatic assist  
4 electrospray, etc., could be assembled into a source in this way.

5 The capillary according to the present invention might also  
6 be used to transport ions from ionization means remote from the  
7 mass spectrometer instrument. This is exemplified by the  
8 embodiment shown in FIG. 9. Depicted in FIG. 9 is an embodiment  
9 of the multiple part capillary according to the invention as used  
10 for integrating a sample preparation robot with an Atmospheric  
11 Pressure Ionization (API) source. Specifically, the system shown  
12 comprises, among other things: robot 90; robot arm 91; sample  
13 tray (not shown); source tray 92; sprayer 93; multiple part  
14 capillary 98 comprising first section 28 having inlet 26, second  
15 section 33 having outlet 34, and union 29; gas transport line 94;  
16 source cover 95; vacuum sub-assembly 96; and mass analyzer 97.

17 Robots such as in the embodiment of FIG. 9 -- for example, a  
18 Gilson 215 Liquid Handler Robot -- consist of a robot arm 91,  
19 which may be used to manipulate samples, "trays" of samples,  
20 sample containers, etc. Robot arm 91 may be used to move  
21 samples, solutions, and reactants from one container (i.e.,  
22 tubes, vials, or microtiter wells, etc.) to another. By mixing  
23 analyte(s), solvent(s), and reactant(s) in a predefined way, the  
24 robot may be used to prepare samples for subsequent analysis.

25 As depicted in FIG. 9, sample spray and ionization occurs

1 within robot 90 and only ions would be transported -- via  
2 multiple part capillary 98 -- to mass analyzer 97. In the  
3 particular embodiment shown, a specially prepared source tray 92  
4 is used. Sample is obtained by robot 90 from a sample tray by  
5 sucking solution into sprayer 93. Robot arm 91 using positioning  
6 means then moves sprayer 93 from source tray 92 to a predefined  
7 location near entrance 26 of capillary 98. Drying gas can be  
8 transported into source tray from vacuum sub-assembly 96 via a  
9 gas transport line 94. The drying gas may be used to assist the  
10 evaporation of the droplets and passage of ions into capillary  
11 98. Sprayer 93 is attached to robot arm 91 and set at ground  
12 potential (of course, any ESI sprayer may be used (e.g.,  
13 pneumatically assisted sprayers with or without pneumatic spray  
14 lines, nanosprayer needles, high voltage sprayers, etc.)), while  
15 inlet 26 to first section 28 of capillary 98 is set at a high  
16 voltage via contact through union 29 and end cap 30A to a power  
17 supply (not shown). This potential difference between sprayer 94  
18 and first section 28 (in addition to pneumatic gas (if using a  
19 pneumatic sprayer)) then induces the spray of the sample solution  
20 and the production of analyte ions.

21       Once the ions enter inlet 26 of capillary 98 they are  
22 carried with a drying gas into the vacuum system of the mass  
23 spectrometer. This may comprise a plurality vacuum chambers 95,  
24 96, 97 connected to differential pumps. Additionally, any number  
25 of ion optical devices (i.e., electrostatic lenses, conventional

1 ion guides, etc.) may be used within the vacuum system to aid in  
2 the transport of the ions to the mass analyzer. Once in the mass  
3 analyzer, the sample ions are analyzed to produce a mass  
4 spectrum. Some of the analyzers which may be used in such a  
5 system include quadrupole, ICR, TOF, etc.

6 The capillary according to the present invention is also  
7 useful in transporting ions from varying locations during  
8 operation. Turning next to FIG. 10, shown is an embodiment of  
9 the multiple part capillary according to the invention as a means  
10 for integrating a sample preparation robot with an elevated  
11 pressure MALDI source for use in mass spectrometry. The system  
12 depicted in FIG. 10 comprises a laser 99, attenuator 100, fiber  
13 optic 101, robot 90 having robot arm 91 for control and movement  
14 of sample probe 102, MALDI sample tray 103, sample holder 104,  
15 alternative embodiment of capillary 98 having first section 105,  
16 second section 33 joined by union 29, ionization source cover 95,  
17 vacuum sub-assembly 96, and mass analyzer 97.

18 The alternative embodiment of the multiple part capillary of  
19 the invention as shown in FIG. 10 comprises a flexible first  
20 section 105 such that its inlet end may be moved by robot arm 91  
21 to various positions for acceptance of the MALDI samples to be  
22 analyzed. As implied by FIG. 10, sample preparation and  
23 ionization may both be performed by robot 90 such that only ions  
24 would be transported through the multiple part capillary 98 to  
25 vacuum sub-assembly 96 and ultimately to mass analyzer 97.



1 Specifically, robot arm has attached to its end sample probe 102,  
2 and fiber optic 101 for directing the laser beam from laser 99  
3 onto sample holder 104 to ionize samples thereon. Alternatively,  
4 mirrors may be used to re-direct the laser beam from laser 99  
5 onto sample holder 104 to ionize samples thereon. Yet another  
6 alternative includes mounting laser 99 onto robot arm 91 or some  
7 other robot arm, which would be able to direct the laser beam  
8 onto the sample. This embodiment also allows for laser 99 to be  
9 easily moved from one location to another with precision. The  
10 ions formed by the laser beam hitting the samples on sample  
11 holder 104 are then carried by the gas flow into and through  
12 capillary 98 to the differential pumping region of vacuum sub-  
13 assembly 96, where additional ion optics (not shown) are designed  
14 to further transport the ions from outlet end of capillary 98 to  
15 mass analyzer 97 for subsequent analysis. Any known ion optics  
16 may be used, including but not limited to, electrostatic  
17 electrodes, RF electrodes, optics of the type referred to in  
18 Franzen et al. U.S. Patent No. 5,663,561 or Whitehouse et al.  
19 U.S. Patent No. 5,652,427, etc.

20 As shown in FIG. 11, which depicts an embodiment of the  
21 multiple part capillary for use with a MALDI probe, the multiple  
22 part capillary according to the invention provides a means for  
23 integrating a sample preparation robot with MALDI mass analysis.  
24 Shown in FIG. 11 are capillary 105, robot arm 91, receptacle 106,  
25 fiber optic 101, and sample plate 104 with raised conical

1 formations 107 onto which samples (not shown) are deposited.  
2 Sample plate 104 and the conical formations form a unitary device  
3 composed of conducting material (e.g., stainless steel). In this  
4 alternate embodiment, capillary section 105 optionally comprises  
5 a specially shaped orifice which fits over cone-shaped sample  
6 holder formations 107 (one at a time) in such a way that gas  
7 flowing through capillary 98 readily captures the ions formed  
8 from the sample by laser desorption ionization. Therefore, the  
9 sample is desorbed directly into the gas flow, thereby resulting  
10 in a minimal loss of ions (i.e., for an efficient transfer of  
11 ions). Alternatively, chemical ionization may be performed in  
12 the capillary or in the vacuum for such efficient transfer of  
13 ions. Optionally, a potential may be applied between sample  
14 carrier 104 and capillary 78 section 105 to help draw ions into  
15 the channel of capillary 78 section 105. Also, fiber optic 101  
16 might be adjusted via piezo electrics or other mechanics to  
17 direct the laser beam to any region of the specific cone-shaped  
18 sample of samples 107 to be ionized. Optionally, this  
19 redirecting of the laser beam may occur during the ionization  
20 process such that ultimately the entire sample is ionized. It is  
21 noted that several laser "shots" may be needed to desorb the  
22 entire sample.

23 While the present invention has been described with  
24 reference to one or more preferred embodiments, such embodiments  
25 are merely exemplary and are not intended to be limiting or

1 represent an exhaustive enumeration of all aspects of the  
2 invention. The scope of the invention, therefore, shall be  
3 defined solely by the following claims. Further, it will be  
4 apparent to those of skill in the art that numerous changes may  
5 be made in such details without departing from the spirit and the  
6 principles of the invention. It should be appreciated that the  
7 present invention is capable of being embodied in other forms  
8 without departing from its essential characteristics.